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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,794	10/31/2003	Giovanni M. Pauletti	3715.17-1	1741

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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

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10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,794	PAULETTI ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-86* is/are pending in the application.

4a) Of the above claim(s) *70-72 and 77-86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-69, 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114, filed 07/18/08.

The filing of this RCE renders the renders the Notice of Appeal, filed 03/21/08, moot.

Status of the Claims

Claims 59-86 are currently pending in this application.

Claims 70-72, and 77-86 are withdrawn for being directed to non-elected subject matter.

Claims 59-69, 73-76 are under examination.

Restriction/Election requirements

Applicant's communication, received 01/26/07, in response to the election requirements, mailed 12/21/06, electing a tampon-like or tampon device as the device species, polyethylene oxide as the polymer species, ketorolac as the anti-inflammatory agent species, vaginal epithelium as the delivery site species for examination purposes is hereby reiterated (see also Office action, mailed 11/21/07).

Terminal Disclaimers

Approval of applicant's terminal disclaimers, received 08/13/07, with respect to copending applications: 10/335,759; 11/180,076; 11/208,209; 11/126,863; 11/522,126; and issued patent 6,982,091, are acknowledged.

Declaration under 37 CFR 1.130

Receipt of the signed declaration of Richard J. D'Augustine is acknowledged. Said declaration is found to be in compliance with 37 CFR 1.68. However, withdrawal of the rejection renders the declaration moot.

Response to applicant's arguments/remarks

Nonstatutory obviousness-type double patenting (ODP) rejection

These rejections are rendered moot by approval of the terminal disclaimers as discussed above.

Rejection under 112, 2nd paragraph

This rejection is rendered moot by the cancellation of the previously pending claims.

Rejection under 102(b)

This rejection is rendered moot by the cancellation of the previously pending claims (see also applicant's Response, filed 07/18/08, at pages 17-27).

Rejection under 103(a)

This rejection is rendered moot by the cancellation of the previously pending claims (see also applicant's Response, filed 07/18/08, pages 27-33).

REJECTIONS

NEW MATTER REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 73 and 74 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention.

Claims 73 and 74 recite the term "α-tocopherol polyethylene glycol succinate." However, applicant has not conveyed possession of the invention with reasonable clarity to one skilled in the art of the common critical pharmaceutical/chemical feature of the genus of antioxidants that would reasonably provide predictable operability of the invention.

To satisfy the written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date, that applicant was in possession of the claimed invention. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the criticality of selecting a particular antioxidant species, especially an undisclosed antioxidant species, in order to predictably practice the invention as claimed. The term "antioxidant," given its broadest reasonable possible interpretation, encompasses a diverse group of compounds which do not share common chemical or pharmaceutical features. In this case, the specification fails to provide literal disclosure for the term "α-tocopherol polyethylene glycol succinate," as well as fail to provide adequate written description to reasonably show that said "α-tocopherol polyethylene glycol succinate" is representative of the claimed genus antioxidants as a whole with respect, for example, pharmaceutical/chemical characteristics. Thus, the term "α-tocopherol polyethylene glycol succinate" is found to constitute new matter because an artisan skilled in the art at the time the invention was made would not have been able to reasonable predict the operability of the invention in

view of the antioxidant species α-tocopherol polyethylene glycol succinate based on the instant written description which fails to show that said species is representative of the genus of antioxidants as a whole.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 62 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69 recites "[t]he polymer film of claim 66 comprising about 14.9%, by weight, polyethylene oxide, about 59.4% of hydroxypropyl methylcelluose, …," which renders the claimed subject matter indefinite because claims 59, 60, and 66, from which claim 69 directly/indirectly depend from, fail to provide adequate antecedent basis for a polymer film comprising two polymer substrates (i.e. polyethylene oxide and hydroxypropyl methylcelluose) because said claims are all directed to a polymer film comprising "a polymer substrate" selected from a Markush group. To the extent that "a" implies a single polymer substrate, the recitation of two polymer substrates in instant claim 69 renders the claimed subject matter indefinite.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1).

This rejection is being made under 103(a) because the teachings of the cited reference do not reasonable envisage the instant relative claimed amounts of the specific ingredients in a transmucosal formulation for vaginal application.

Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1) transmucosal device film or films (in the case of co-extrusion or layering = film sheet) comprising at least one water-soluble, water-swellable or water-insoluble thermoplastic **polymer** such as, but not limited to, hydroxypropycellulose, polyethylene oxide, ..., and hydroxymethyl cellulose); one or more canniboid medicaments (= therapeutic agent); a bioadhevise, such as water-soluble or water swellable polymers derived from acrylic acid or a pharmaceutically acceptable salt thereof, including polyacrylic acid polymers (e.g. carbomers, polycarbophils and/or water-soluble salts of a cop-polymer of methyl vinyl ether and maleic acid or anhydride); one or more **pH adjusting agents** to improve stability and solubility (e.g. potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate, ethanolamine, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide); and other additives, including **penetration enhancers**, and/or hydrophobic polymers, cross-linking agents to, for example reduce matrix erosion time (e.g. an organic acid such as tartaric acid, alpha-hydroxy acid, citric acid, fumaric acid, succinic acid), to render the film useful for transmucosal application (para. 0021-0039). Elsohly et al. teach that the transmucosal preparation may also contain other components that modify the extrusion, molding, or casting characteristics or physical properties of the matrix, including, for example, **polyethylene**, xylitol, sucrose, surface-active agents, ...,

and combinations thereof (para. 0026). Elsohly et al. teach transmucosal preparations may comprise super-disintegrants or absorbents e.g. sodium starch glycolate (Explotab or Primojel), croscarmellose sodium (Ac-Di-Sol), cross-linked PVP (Polyplasdone XL 10), clays, alginates, corn starch, potato starch, pregelatinized starch, modified starch, cellulosic agents, ..., gums,..., and other disintegrants known to those of ordinary skill in the art (para. 0027); transmucosal preparation may also contain an antioxidant (e.g. **sodium metabilsulfate**, sodium bisulfite, **vitamin E and its derivatives**), chelating agent (e.g. EDTA, polycarboxylic acids, polyamines, and derivatives thereof), stabilizer, **surfactant** (e.g. sucrose stearate, vitamin E deriviatives, sodium lauryl sulfate, dioctyl sodium sulfosuccinate), preservative (e.g. methyl paraben) , ..., flavor, colorant, fragrance and combinations thereof (paras. 0028-0039). Elsohly et al. teach that transmucosal preparations that provide a controlled release of an agent, wherein said preparation contain a suitable release rate modifier, wherein said suitable **release rate modifier** include: poly (ethylene oxide) or PEO; hydroxypropyl methylcellulose (HPMC); ..., polycarbophil, carbomer or a polysaccharide (para. 0038). Elsohly et al. teach that preferably said transmucosal formulations comprise a **penetration enhancer**, which may also be referred to as an absorption enhancer or permeability enhancer, which may include bile salts (e.g. sodium deoxycholate), **surfactants** (e.g. sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetyl chloride, and polyoxyethylene monoalkylethers), benzoid acids (e.g. sodium salicylate, methoxy salicylate), fatty acids (e.g. lauric acid, oleic acid, undecanoic acid and methyl oleate), fatty alcohols (e.g. octanol, nonanol), laurocapram, polyols (e.g. propylene glycol,

glycerin), cyclodextrins, sulfoxides (e.g. dimethyl sulfoxide and dodecyl methyl sulfoxide), terpenes (e.g. menthol, thymol, and limonene), urea, chitosan and other natural and synthetic polymers; polyoxyethylene monoalkylethers include Brij® and Myrj® series (paras. 0016 , 0033). Elsohly et al. teach a method for increasing the permeability of a patient's mucosa by including a permability enhancement agent in the transmucosal formulation, wherein said permeability enhancement agent is PEG 400, and/or other enhancers in which cannabinoids may be solubilized; useful solubilizers which may inherently be penetration or absorption enhancers, include, for example, polyethylene glycol (PEG), propylene glycol, Dibutyl subacetate, Glycerol, Diethyl phthalate (phthalate esters), triacetin, citrate esters-triethyl citrate (TEC), acetyltriethyl citrate (ATEC), tributyl citrate (TBC), acetyltributyl citrate (ATBC), benzyl benzoate, sorbitol, xylitol, Miglyol (glycerides), bis(2-ethyllhexyl) adipate, mineral oil, polyhydric alcohols such as glycerin and sorbitol, glycerol esters such as glycerol, triacetate; fatty acid triglycerides such as NEOBEE* M-5 and mineral oil, vegetable oils such as castor oil, etc., polyoxyethylene sorbitan, fatty acid esters such as TWEENS, polyoxyethylene monoalkyl ethers such as **BRIJ** and MYRJ series, sucrose monoesters, lanolin esters, lanolin ether, and **chitosan** and other natural and synthetic polymers (paras. 0014-0016). Also included as solubilizers for the cannabinoids are organic solvents, such as ethanol, benzene and the like, which may be utilized in solvent cast techniques (para. 0014). Elsohly et al. exemplify transmucosal formulations comprising polyethylene oxide (PEO i.e. applicant's elected polymer species) in amounts ranging from **10%-80.4%** (para. 0043-0053, including Examples 2-6, and Tables I and III). Elsohly et al.

also **exemplify transmucosal formulations** comprising PEO (10-13%; i.e. polymer substrate), PEG 400 (8-12%; i.e. absorption enhancer/solubilizer/penetration enhancer), citric acid (0.5%), sodium dexoycholate (5% = permeability enhancer/penetration enhancer), methyl paraben (0.2%), **THC (8-16% = therapeutic agent = anti-migraine/non-steroidal anti-inflammatory agent/anti-nausea agent**), hydroxypropyl cellulose (55.23-63.23%), polyvinylpuyrrolidone 10%, butylated hydroxyl toluene (0.05%), and carbomer (5%). See page 6, para 0051, Table 1). Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1) teach methods for preparing transmucosal formulations via, for example, hot-melt extrusion, hot-melt molding, by admixing or utlilizing a solvent cast technique, and wherein an effective amount of a cannabinoid is incorporated into the transmucosal cannabinoid-containing preparation, and wherein said transmucosal formulation include a matrix patch for retaining and dispersing the active ingredients (para. 0015). Elsohly et al. teach formulations comprising a bioadhesive system that is an effective, feasible, and convenient intra-oral drug delivery system for applying and delivering controlled dosages of cannabinoids through or into the oral cavity, which may also be extended top controlled drug delivery in gynecological (vaginal), nasal, sinus, and ophthalmic applications (para. 0019). Elsohly et al. teach single and multi-layered laminated (= sheet) film matrix containing cannabinoids, wherein said matrix can be cut or formed into almost unlimited shapes and sizes, depending on the application and dosage intended (para. 0020). In addition, Elsohly et al. teach that cannabinoids (i.e. non-steroidal anti-inflammatory agents) have various **medicinal uses**, including treatment of nausea (= anti-nausea agent), pain,

migraines (i.e. anti-migraine agent), and rheumatic (i.e. anti-inflammatory effect) and osteo-arthritis (i.e. anti-inflammatory effect), muscle dysfunction associated with multiple sclerosis. (para. 0006). Elsohly et al. also exemplify transmucosal formulations comprising vitamin E TPGS (=α-tocopherol polyethylene glycol succinate; see para. 0048, Examples 5 and 6).

This rejection is being made under 103(a) because one of skill in the art would not immediately envisage the combination of components as claimed.

It would have been obvious to a person of skill in the art at the time the invention was made prepare a transmuscosal preparation comprising a polymer substrate (e.g. PEO), an anti-migraine agent/anti-nausea agent/non-steroidal anti-inflammatory agent (e.g. THC), a penetration enhancer (e.g. PEG 400), a plasticizer (e.g. propylene glycol), a surfactant (e.g. sodium lauryl sulfate), wherein said transmucosal formulation is in the form of a polymer film sheet for topical application of said anti-migraine agent/anti-nausea agent/non-steroidal anti-inflammatory agent (i.e. THC) to the vaginal epithelium to control pain as taught by Elsohly et al. One would have been motivated to prepare a transmucosal preparation to control pain because Elsohly et al. suggest that transmucosal preparation comprising THC may be useful for treating various conditions, including migraine and arthritis. One would have expected to successfully create said transmucosal formulation because Elsohly et al. teach transmucosal formulations for gynecological/vaginal application.

It is noted that the term "non-steroidal anti-inflammatory agent" given its broadest reasonable possible interpretation is construed to encompass all non-steroidal drugs to exhibit anti-inflammatory activity, including non-steroidal drugs used for treating arthritis e.g. THC and its derivatives as taught by Elsohly et al.

It is noted that the instant claimed polymer substrates (e.g. PEO), penetration enhancers (e.g. dioctyl sodium sulfosuccinate, chitosan), plasticizers (e.g. PEG), and surfactants (e.g. polysorbate 80, and sodium lauryl sulfate) overlap with the teachings of the above cited references.

In addition, instant claimed amounts of the therapeutic agent (from about 0.1 to about 2000mg), polymer substrate (from about 2% to about 100%), penetration enhancer (from about 0.1 to about 60%), plasticizer (from about 5% to about 25%), and surfactant (from about 0.01% to about 5%), all overlap with the teaching of the above cited art (paras. 0043-0053, including Examples 2-6, and Tables I and III).

Thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Claims 60-69, and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1), in view of McCoy et al. (US Patent 6,495,120 B2), as evidenced by National Library of Medicine - Medical Subject Headings –TPGS alpha-tocopherol polyethylene glycol siccinate. 2008, page 1.

The rejection under 112, 2nd is noted.

The above discussion of Elsohly et al. is incorporated by reference. Elsohly et al. do not teach keterolac.

Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1) teach transmucosal device film or films (in the case of co-extrusion or layering = film sheet) comprising at least one water-soluble, water-swellable or water-insoluble thermoplastic **polymer** such as, but not limited to, hydroxypropycellulose, polyethylene oxide, ..., and hydroxymethyl cellulose); one or more canniboid medicaments; a bioadhevise, such as water-soluble or water swellable polymers derived from acrylic acid or a pharmaceutically acceptable salt thereof, including polyacrylic acid polymers (e.g. carbomers, polycarbophils and/or water-soluble salts of a cop-polymer of methyl vinyl ether and maleic acid or anhydride); one or more **pH adjusting agents** to improve stability and solubility (e.g. potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate, ethanolamine, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide); and other additives, including **penetration enhancers**, and/or hydrophobic polymers, cross-linking agents to, for example reduce matrix erosion time (e.g. an organic acid such as tartaric acid, alpha-hydroxy acid, citric acid, fumaric acid, succinic acid), to render the film useful for transmucosal application (para. 0021-0039). Elsohly et al. teach that the transmucosal preparation may also contain other components that modify the extrusion, molding, or casting characteristics or physical properties of the matrix, including, for example, **polyethylene**, xylitol, sucrose, surface-active agents, ...,

and combinations thereof (para. 0026). Elsohly et al. teach transmucosal preparations may comprise super-disintegrants or absorbents e.g. sodium starch glycolate (Explotab or Primojel), croscarmellose sodium (Ac-Di-Sol), cross-linked PVP (Polyplasdone XL 10), clays, alginates, corn starch, potato starch, pregelatinized starch, modified starch, cellulosic agents, ..., gums,..., and other disintegrants known to those of ordinary skill in the art (para. 0027); transmucosal preparation may also contain an antioxidant (e.g. **sodium metabilsulfate**, sodium bisulfite, **vitamine E and its derivatives**), chelating agent (e.g. EDTA, polycarboxylic acids, polyamines, and derivatives thereof), stabilizer, **surfactant** (e.g. sucrose stearate, vitamin E deriviatives, sodium lauryl sulfate, dioctyl sodium sulfosuccinate), preservative (e.g. methyl paraben) , ..., flavor, colorant, fragrance and combinations thereof (paras. 0028-0039). Elsohly et al. teach that transmucosal preparations that provide a controlled release of an agent, wherein said preparation contain a suitable release rate modifier, wherein said suitable **release rate modifier** include: poly (ethylene oxide) or PEO; hydroxypropyl methylcellulose (HPMC); ..., polycarbophil, carbomer or a polysaccharide (para. 0038). Elsohly et al. teach that preferably said transmucosal formulations comprise a **penetration enhancer**, which may also be referred to as an absorption enhancer or permeability enhancer, which may include bile salts (e.g. sodium deoxycholate), **surfactants** (e.g. sodium lauryl sulfate, polysorbate 80, laureth-9, benzalkonium chloride, cetyl chloride, and polyoxyethylene monoalkylethers), benzoid acids (e.g. sodium salicylate, methoxy salicylate), fatty acids (e.g. lauric acid, oleic acid, undecanoic acid and methyl oleate), fatty alcohols (e.g. octanol, nonanol), laurocapram, polyols (e.g. propylene glycol,

glycerin), cyclodextrins, sulfoxides (e.g. dimethyl sulfoxide and dodecyl methyl sulfoxide), terpenes (e.g. menthol, thymol, and limonene), urea, chitosan and other natural and synthetic polymers; polyoxyethylene monoalkylethers include Brij® and Myrj® series (paras. 0016 , 0033). Elsohly et al. teach a method for increasing the permeability of a patient's mucosa by including a permability enhancement agent in the transmucosal formulation, wherein said permeability enhancement agent is PEG 400, and/or other enhancers in which cannabinoids may be solubilized; useful solubilizers which may inherently be penetration or absorption enhancers, include, for example, polyethylene glycol (PEG), propylene glycol, Dibutyl subacetate, Glycerol, Diethyl phthalate (phthalate esters), triacetin, citrate esters-triethyl citrate (TEC), acetyltriethyl citrate (ATEC), tributyl citrate (TBC), acetyltributyl citrate (ATBC), benzyl benzoate, sorbitol, xylitol, Miglyol (glycerides), bis(2-ethyllhexyl) adipate, mineral oil, polyhydric alcohols such as glycerin and sorbitol, glycerol esters such as glycerol, triacetate; fatty acid triglycerides such as NEOBEE* M-5 and mineral oil, vegetable oils such as castor oil, etc., polyoxyethylene sorbitan, fatty acid esters such as TWEENS, polyoxyethylene monoalkyl ethers such as **BRIJ** and MYRJ series, sucrose monoesters, lanolin esters, lanolin ether, and **chitosan** and other natural and synthetic polymers (paras. 0014-0016). Also included as solubilizers for the cannabinoids are organic solvents, such as ethanol, benzene and the like, which may be utilized in solvent cast techniques (para. 0014). Elsohly et al. exemplify transmucosal formulations comprising polyethylene oxide (PEO i.e. applicant's elected polymer species) in amounts ranging from **10%-80.4%** (para. 0043-0053, including Examples 2-6, and Tables I and III). Elsohly et al.

also **exemplify transmucosal formulations** comprising PEO (10-13%; i.e. polymer substrate), PEG 400 (8-12%; i.e. absorption enhancer/solubilizer/penetration enhancer), citric acid (0.5%), sodium dexoycholate (5% = permeability enhancer/penetration enhancer), methyl paraben (0.2%), THC (8-16% = therapeutic agent = anti-migraine/non-steroidal anti-inflammatory agent/anti-nausea agent), hydroxypropyl cellulose (55.23-63.23%), polyvinylpuyrrolidone 10%, butylated hydroxyl toluene (0.05%), and carbomer (5%). See page 6, para 0051, Table 1). Elsohly et al. (US Patent Application Pub. No. 2006/0257463 A1) teach methods for preparing transmucosal formulations via, for example, hot-melt extrusion, hot-melt molding, by admixing or utlilizing a solvent cast technique, and wherein an effective amount of a cannabinoid is incorporated into the transmucosal cannabinoid-containing preparation, and wherein said transmucosal formulation include a matrix patch for retaining and dispersing the active ingredients (para. 0015). Elsohly et al. teach formulations comprising a bioadhesive system that is an effective, feasible, and convenient intra-oral drug delivery system for applying and delivering controlled dosages of cannabinoids through or into the oral cavity, which may also be extended top controlled drug delivery in gynecological (vaginal), nasal, sinus, and ophthalmic applications (para. 0019). Elsohly et al. teach single and multi-layered laminated (= sheet) film matrix containing cannabinoids, wherein said matrix can be cut or formed into almost unlimited shapes and sizes, depending on the application and dosage intended (para. 0020). In addition, Elsohly et al. teach that cannabinoids (i.e. non-steroidal anti-inflammatory agents) have various **medicinal uses**, including treatment of nausea (= anti-nausea agent), pain,

migraines (i.e. anti-migraine agent), and rheumatic (i.e. anti-inflammatory effect) and osteo-arthritis (i.e. anti-inflammatory effect), muscle dysfunction associated with multiple sclerosis. (para. 0006). Elsohly et al. also exemplify transmucosal formulations comprising vitamin E TPGS (=α-tocopherol polyethylene glycol succinate; see para. 0048, Examples 5 and 6).

However, Elsohly et al. do not teach NSAIDS (e.g. keterolac).

McCoy et al. (US Patent 6,495,120 B2) McCoy et al. teach formulations that may comprise one or more analgesics as the pharmaceutical agent, including non-narcotic analgesics such as ketorolac and salts thereof (= applicant's elected compound species) for use in controlling pain (col. 3, lines 46-54). McCoy et al. teach exemplary embodiments comprising sodium lauryl sulfate in amounts of 0.9 to 1.2% by weight (col. 4, lines 32-34). McCoy et al. teach stable intra-oral formulations for intra-oral delivery to a patient of a pharmaceutical agent, wherein said formulation comprises a pharmaceutical agent mixed with an orally-acceptable oral absorption enhancer in a orally-acceptable carrier-solvent, wherein the oral-absorption enhancer is adapted to modify the surface membrane such that absorption through the surface membrane is initiated or increased, and wherein the **oral-absorption enhance**r may comprise hydroxypropyl-beta-cyclodextrin and surfactants, including polysorbate 80, sodium lauryl sulfate, Brig surfactants, Tween and Pluronic surfactants (abstract; col. 4, lines 10-34). Mccoy et al. teach formulations, wherein the pharmaceutical agent is present in an amount of about 0.01 to 25% by weight (col. 3, lines 56-59). Also, McCoy et al. teach that the concentration of oral-absorption enhancers (e.g. polysorbate 80, sodium

lauryl sulfate,) will vary with the particular pharmaceutical agents and/or method of delivery, but typically said oral-absorption enhancers will be present in amounts up to 50% by weight (col. 4, line 27-34).

With respect to the term "α-tocopherol polyethylene glycol succinate" as recited in claims 73 and 74, it is noted that the term "Vitamin E TPGS" as taught by Elsohly et al. means α-tocopherol polyethylene glycol succinate as evidenced by the National Library of Medicine - Medical Subject Headings – 2008 (see also attached Form 892).

It would have been obvious to a person of skill in the art to add ketorolac or its salts thereof as taught by McCoy et al. to the transmusocal formulation polymeric film for vaginal application as taught by Elsohly et al. for additive pain/analgesic effect. One would have been motivated to add ketorolac or any of its salts thereof to said transmucosal formulation for additive analgesic/pain effects because Elsohly et al. teach transmucosal formulations comprising analgesic agents (i.e. THC) and keterolac is also an analgesic agent (Cf. In re Kerkhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). One would have expected to successfully add keterolac, and additional optional agents (e. g. BHA or vitamin E TPGS) for delivery of said therapeutic agents to the vaginal epithelium to the transmucosal formulation polymeric film for control pain because Elsohly et al. teach transmucosal formulations for intra-oral and gynecological/vaginal applications and both Elsohly et al. and McCoy et al. teach intra-oral transmucosal drug delivery formulations for enhancing the transmucosal delivery analgesic pharmaceutical agents.

It is noted that the instant claimed polymer substrates (e.g. PEO), penetration enhancers (e.g. dioctyl sodium sulfosuccinate, chitosan), plasticizers (e.g. PEG), surfactants (e.g. polysorbate 80, and sodium lauryl sulfate), buffer agents (e.g. sodium bicarbonate) overlap with the teachings of the above cited references. Also, the instant limitation with respect to the thickness of the polymer film of "from 0.5 mm to about 2 mm layer" also overlaps with the teaching of the transmucosal preparations of approximately 1 mm thickness taught by Elsohly et al. (para. 0047; see instant claim 75). The instant terms "butylated hydroxyanisole (BHA)" (see claims 67 and 69) and α-tocopherol polyethylene glycol succinate (see instant claims 73 and 74) also overlap with the teaching of Elsohly et al. (paras. 0037, and 0047-0048).

With respect to the instant claimed combination of PEO and hydroxypropyl methylcellulose (see instant claim 67), it is noted that Elsohly et al. exemplify transmucosal formulations comprising both PEO and hydroxypropyl methylcellulose (para. 0043, Example 1; see instant claim 67).

In addition, instant claimed amounts of the therapeutic agent (from about 0.1 to about 2000mg), polymer substrate (from about 2% to about 100%), penetration enhancer (from about 0.1 to about 60%), plasticizer (from about 5% to about 25%), and surfactant (from about 0.01% to about 5%), all overlap with the teaching of the above cited art (paras. 0043-0053, including Examples 2-6, and Tables I and III).

It is also noted that based on the teaching of Elsohly et al. that solubilizers (e.g. PEG 4000, propylene glycol, Brij, glycerin, triacetin) may function inherently as penetration or absorption enhancers; see para. 0014), it would have been obvious to a

person of skill in the art at the time the invention was made to use a solubilizer (e.g. PEG 400) for its dual purpose as an penetration/permeability enhancer and as a solubilizer (i.e. plasticizer) to increase the solubility of the ingredients in the transmucosal formulation. Similarly, it would have been person of skill in the art at the time the invention was made to use a surfactants such as sodium lauryl sulfate, sodium dexoycholate, polysorbate 80 for their dual effects as surfactants and penetration/permeability enhancers (see para. 0016).

It is noted that the term "said penetration enhancer ... present in from about 60%, by weight," as recited in claim 62 reads on the term "up to 50% by weight of oral-absorption enhancers" as taught by McCoy et al. (col. 4, line 27-34) because Elsohly et al. teach that penetration enhancers (also referred to as absorption enhancers) may include surfactants such as polysorbate 80, sodium lauryl sulfate (para. 0016). As discussed previously, it is the examiner's position that it would have been within the scope of knowledge and skill of an artisan skilled in the art at the time the invention was made to adjust the relative amounts of the various pharmaceutical ingredients in the transmucosal formulation, including adjusting the amount of the penetration enhancer to an amount of 60% by weight, in order to prepare a stable transmucosal formulation. Besides, McCoy et al. teach that the concentration of oral-absorption enhancers (e.g. polysorbate 80 and sodium lauryl sulfate) will vary with the particular pharmaceutical agents and/or method of delivery (col. 4, line 27-34).

It is the examiner's position that it would have been within the scope of skill and knowledge of an artisan skilled in the art at the time the invention was made to

manipulate the release rate of the transmucosal formulation taught by the prior art to arrive at release rates e.g. a release rate of 50% within 80 minutes = claim 66; and release rates from about 2% to about 7.3%/minute = claims 68 and 70. Further, to the extent that the prior art teaches transmucosal formulations wherein the absorption enhancers (e.g. sodium lauryl sulfate) as well as the amount of said absorption enhancers overlap with the instant permeability enhancers and amount of instant permeability enhancers in the formulations encompassed by the instant claims, one would reasonably expect the transmucosal formulations taught by the prior art to have similar release rates as the instant claimed formulations (In re Spada).

Thus, a person of skill in the art at the time the invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Relevant Art of Record

The below prior art references made of record and relied upon are considered pertinent to applicant's invention.

Hall et al. (US Patent 5,545,407) dermatological compositions comprising vitamin E compounds i.e. tocopherols, including tocopherol derivatives such as tocopheryl polyethylene glycol 1000 succinate, wherein said vitamin E compound (e.g. tocopheryl polyethylene glycol 1000 succinate) present in amounts of from about 0.05 to about 20%, for example, renders the composition non-irritating or reduces the skin irritating effects of the composition (abstract; col. 5, line 51 to col. 6, line 20; see reference claim 7). Hall et al. also teach that said compositions can comprise a wide range of additional cosmetic and pharmaceutical ingredients commonly used in the skin care industry, and

as described in the *CTFA Cosmetic Ingredient Handbook*, Second edition, 1992, including absorbents, abrasives, acne agents, antimicrobial agents, antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers, fragrance components, humectants, opacifying agents, pH adjusters, plasticizers, preservatives, propellants, reducing agents, skin bleaching agents, skin-conditioning agents (e.g. emollient, humectants), skin protectants, solvents, surfactants (e.g. cleansing agents, emulsifying agents, foam boosters, hydrotropes, solubilizing agents, and suspending agents), nonsurfactant suspending agents, sunscreen agents, ultraviolet light absorbers, and viscosity increasing agents (col. 9, line 46 to col. 10, line 51).

Kumar et al. (Kumar et al. Pharmaceutical Polymeric Controlled Drug Delivery Systems. Advances in Polymer Science. 2002; 160: 45-117) teach that even though the concept of drug delivery systems is not new, great progress has been made in treating a variety diseases using newly developed formulations, including polymeric drug delivery systems (e.g. film and membranes)for delivering various drugs to a targeted point to deliver a drug to deseased lesions (see abstract; and especially pages 92-94).

Samour et al. (US Patent 5,807,957; already made of record) teach lipophilic or amphiphilic or hydrophilic film-forming polymers for use individually or in combination as a delivery system for delivering pharmacological or cosmetic agents to the skin or hair; the disclosed film-forming amphilic polymers include: polyethylene glycol methyl ether, polyethylene glycol butyl ether, ethoxyethoxyehtanol, polyethylene glycol,

methylenedicyclohexy, methylenedicycloheyxl and hexamethylene (abstract; col. 17, lines 9-51, and col. 1, line 56 to col. 19, line 10, including Examples 1-8). Samour et al. teach compositions comprising suitable penetration enhancers to facilitate penetration through the stratum corneum and epidermis layers into and through the dermal layer and blood stream in combination with pharmacological dermatological agents and the film-forming polymer is also taught (col. 17, lines 9-51).

Jellum et al. (US Patent 7,241,460; already made of record) teach skin penetration enhancing agents, including propylene glycol laurate, propylene glycol, alcohols (e.g. ethanol, isopropanol, essential oils, Tween 80 and other surfactants (col. 4, lines 46-57); and bioadhesive (i.e. mucoadheisve) agents, including natural or synthetic, polyanionic, polycatuonic or neutral (col. 5, line 5 to col. 6, line 6). Jellum et al. teach that preferred bioadhesive agents include polyacrylic hydrogels, chitosan, polyvinyl alcohol, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose, sodium alginate, scleroglucan, xanthum gum, pectin, Orabse and polygalactonic acid (col. 6, lines 12-15). Jellum et al. also teach polymeric bioadhesives may be crosslinked and be in the form of copolymers e.g. poly(acrylic acid) polymers (or copolymers) – a polycarbophil e.g. Carbomer (Carbopol) (col. 6, lines 1-11).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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16 October 2008

/C. R./

Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611